REMARKS

1. We thank the examiner for indicating that claim 46 (a polypeptide which comprises the amino acid sequence of SEQ ID NO:2) is allowable. However, we respectfully submit that applicant is entitled to broader protection.

2. Claims 50-61 are new. The basis for claims 50-56 is addressed within the discussion of the written description rejection. New claims 57-62 are based on clauses (a) and (b) of original claim 4.

Claim 4, the first independent claim, has been amended to move certain limitations into new dependent claims 57-61.

3. The sole rejection in this case is to the effect that claims 4, 6-10, 43-45 and 47-49 do not satisfy the written description requirement.

Claim 4 is directed to the following subject matter

> A purified or non-naturally occurring mutant polypeptide comprising an amino acid sequence which is at least 96% identical to the retroviral envelope polypeptide amino acid sequence shown in SEQ ID NO: 2, with percentage identity calculated relative to the full length of SEQ ID NO:2, wherein said polypeptide is
>
> a) capable of mediating infection of a cell by use of the polytropic/xenotropic receptor encoded by the Rmc1 locus of the NIH Swiss inbred NFS/N mouse for entry and unable of mediating infection of a cell by use of a human polytropic/xenotropic receptor encoded by the human RMC1 locus or
>
> b) capable of mediating infection of a human cell, and wherein said polypeptide of (b) differs from SEQ ID NO:2 by at least one substitution in the VR3 region of SEQ ID NO:2.

Independent claim 9 recites a minimum identity of at least 95%, rather than 96%, and further requires that "said polypeptide differs from SEQ ID NO:2 at least by substitution at position 212 in SEQ ID NO:2 with methionine[1]. Independent claim 48 likewise requires "only" 95% identity, but also requires that the polypeptide "comprise a subsequence identical to the VR3 region (amino acids 199-213) of SEQ ID NO:2.

The examiner concedes that there is written description for SEQ ID NO:2, as evidenced by the treatment of claim 46. The examiner also concedes that there is written description for double mutants at positions 212/213, such as those set forth in Table 8.

However, the examiner argues that "the specification fails to provide a structure to function correlation which supports the wide scope of different polypeptides claimed", i.e. whether the reduced-to-practice species are, in the light of applicant's teachings, representative of the claimed genus.

With regard to the scope of the genus, the examiner points out that since the reference sequence (SID 2) is 639 amino acids a sequence that is "only at least 95% identical" could have up to 32 amino acid differences from SID 2, and that "as claimed", the differing amino acid may occur at any position of the sequence and be any one of the other 20 amino acids.

We take up this last point first. In the original[2] written description training materials (Mach 1, 2000) the PTO indicated (example 14) that a claim to a polypeptide having at least 95% identity to an identified reference sequence, and retaining the enzymatic activity of the latter, had written description. The PTO explained that because of the structural (95% identity) and functional (catalytic activity) limitations, that genus "does not have substantial variation". The PTO noted that site-specific

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[1] Cp. claim 49, dependent on claim 4.

[2] We will discuss the revision in due course; it was concerned with the impact of the activity limitation.

mutagenesis is conventional and it assumed that the specification disclosed an assay for the recited activity.

The PTO, in drafting this example, was surely aware that the model claim did not limit the mutation to any particular positions of the sequence, or to any particular replacement amino acids[3]. It also was surely aware that it was possible that a single substitution, in some positions, would abolish activity.

We believe that the PTO reasoning was that (1) most mutations (and especially those that would be chosen by a skilled worker attempting to preserve utility) would not abolish activity, (2) that mutations are usually additive in their effects, and (3) the cumulative effect of mutating 5% of the molecule, given (1) and (2), would usually not abolish activity.

We appreciate that the PTO may have had in mind a smaller protein than SID 2. However, the median length of a human protein is 375 aa, and that of a eukaryotic metabolic protein is 494 aa (Brochieri, et al. 2005) (Exhibit 1). We are not in a position to analyze the length distribution of the USPTO sequence database as of 2000, but we suspect that claims reciting proteins with a length of about 400 a.a. were not unusual. At that size level, 95% identity would permit 20 amino acid differences. Even if the PTO had in mind a protein similar in size to say Human Growth Hormone (191 aa), that would still permit about 10 amino acid differences.

Given this background, even if the examiner could fairly question whether the original WDTM would have accepted conservation of just 95% of a 63 a aa sequence, the examiner cannot fairly question the dependent claims reciting 96-99%. These tolerate fewer amino acid differences

[3] This was explicitly acknowledged in the revised WDTM Example 11B, p. 40.

Claim	Required %	Permitted Diffs
9	95%	31[4]
4	96%	25
43	97%	19
44	98%	12
45	99%	6
50	99.5%	3

As we can see from the table, the number of differences (19) that claim 43 (97%) identity) permits in mutating a 63a aa protein is less than what the "standard" WDTM 95% identity limitation would permit (20) in an average (400 aa) protein. And claims 44 (98%), 45 (99%) and new claim 50 (99.5%) (basis at P7, L18) are even more stringent.

We next turn our attention to the revised Written Description Training Materials (Revision 1; March 25, 2008).

Revised WDTM Ex. 10 Claim 2 read "An isolated variant of a protein comprising the amino acid sequence shown in SEQ ID NO: 3, wherein the variant comprises an amino acid sequence that is at least 95% identical to SEQ ID NO 3." Whereas Claim 3 read, "The isolated variant of claim 2, wherein the variant catalyzes the reaction A->B."

The distinction, of course, is that WDTM claim 2 defines the claimed variant solely by structure, whereas WDTM claim 3 additionally imposes a functional limitation. The PTO, through the revised WDTM, now reads an activity limitation as triggering a greater scrutiny into what applicant discloses concerning structure-activity relationships.

While the WDTM doesn't cite a case, we believe that the new doctrine that an activity limitation requires an additional

[4] If there were 32 differences, the identity would be 94.99%, which is less than 95%.

showing is derived from *Ex parte Porro* (BPAI March 11, 2008), text available online at
http://www.uspto.gov/web/offices/dcom/bpai/its/fd080184.pdf

Note that Porro was published as an "informative opinion". That means it is not precedential but is considered to be "useful guidance". The three types of opinions are described in http://www.uspto.gov/web/offices/dcom/bpai/sop2.pdf

Since Porro is not precedential, it may fairly be contended that the proper interpretation of the written description requirement is that embodied in the original WDTM example 10, which encouraged combining a percentage identity limitation with an activity limitation.

However, we will proceed on the assumption that the revised WDTM is controlling.

Revised WDTM Example 10, in discussing the model claim 3, assumes (1) there is no teaching in the specification regarding which 5% of the structure can be varied while retaining the ability of the protein to catalyze the reaction A->B, and (2) there is no art-recognized correlation between structures other than SID 3 and this activity, whereby those skilled in the art could predict which amino acids could be varied from SID 3 without loss of the catalytic activity. Hence, it concludes that model claim 3 lacks WD.

This analysis is extended in examples 11A and 11B, wherein the percentage identity required is only 85% and the referenced activity is a generic "activity X". Example 11A concedes WD for a pure **85%** (not 95!) identity claim, and the logic of the example would appear to apply to claims with lower minima, at least if they required more than 50% identity (see technical note regarding conservation of tertiary structure, bottom of page 38).

In WDTM EX. 11A, model claim 2, with the activity limitation, is held to lack WD because the spec is assumed to fail to meet the two part test mentioned above.

On the other hand, in WDTM Ex. 11B model claim 2, the activity limitation was held to be proper because the

specification identified as such the binding domain and catalytic domain responsible for the activity, and suggested that conservative mutations in those domains would preserve the activity.

We therefore turn to a discussion of what our specification teaches with regard to the correlation between the structure of the mutant polypeptide, and activities (a) and (b) of claim 4[5].

The present invention relates to the envelope polypeptide of the purified murine leukemia virus (MLV) strain SL3-2, which is able to mediate infection of mouse cells but not human cells (P4, L16-26), or a non-naturally occurring mutant thereof.

As described on page 1, lines 15-19:

> Murine Leukaemia viruses are a family of simple retroviruses isolated from laboratory mice. Retroviruses carry their genomes as two copies of a single RNA molecule and the simplest retroviruses contain the *gag*, *pro*, *pol* and *env* genes. These genes are found in the same order in all known retroviruses, reflecting the phylogenetic relationship of retroviruses.

The envelope protein "consists of two subunits: the transmembrane (TM) and the surface unit (SU). The function of the envelope protein is binding of the virus to its target cell and mediating fusion of the virus and cellular membranes". (P1, L30-33).

The sequences of a large number of MLV envelope proteins are known and 29 MLVs, besides the instantly sequenced SL3-2, are listed in Fig. 1. While only the portions of those sequences that are homologous with what we call the VR-3 region (P7, L22-35) of SEQ ID NO:2 are expressly recited, Fig. 1 acts as a clear "blazemark" to the skilled worker that they should consider these

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[5] The analysis may be extended, mutatis mutandis, to claims 7 and 10, which have activity limitations.

sequences. Methods of aligning their sequences with SEQ ID NO:2 are discussed at P6, L23 to P7, L2, and were clearly used by the inventors as revealed at P7, L22-35:

> In a sequence alignment between SL3-2 and MCF-247, three regions display differences in the amino acid sequence, as described in example 3 and figure 1 and 2. Two of these regions correspond to parts of the variable VRA and VRB regions, whereas the third is a 15 amino acids long stretch upstream of the proline rich region. The present inventors have named this region VR3.
>
> VR3 region
> Further, a sequence alignment of MLVs from different sub-families show conserved amino acids at positions 203-208 WGLRLY and at positions 214-215 DP based on SL3-2 sequence, thus defining a 13 amino acid stretch of SEQ ID NO:2.
>
> In the present context, the term "VR3 region" comprises all of the amino acids found between the residue found at two positions after the conserved tryptophan 197 and the residue before the conserved aspartic acid 214 (according to the sequence shown in SEQ ID NO:2) including these two positions.

Note that it is clear from the quoted passage that the variability (among MLB) of the VRA and VRB regions was already recognized in the art, and also there is an implication that the "proline rich region" is a conserved region.

It would be clear to a person skilled in the art that

mutation of residues that are conserved among MLV envelope polypeptides, especially replacement of amino acids with dissimilar amino acids[6], would be more likely to disrupt the basic function of the envelope protein, i.e., its ability to encapsulate the retroviral genetic material, perhaps by interference with overall protein folding.

SL3-2 is unable to infect human cells (P4, L16-19), whereas amphotrophic MLVs, such as MCF-247, do infect human cells (P2, L3-4; P5, L29-33; P8, L7-12).

Hence, it is clear that this difference in tropism must be attributable to sequence differences between SL3-2 envelope and the amphotrophic MLV (including MCF-247) envelopes. As stated at P7, L22-25, previously quoted, the sequence differences are concentrated in three regions, denominated VRA, VRB and VR3.

The location of the VRA and VRB (as well as VR3 regions) within both SL3-2 and MCF-247 are plainly marked on Fig. 2 and hence these regions can be readily be identified in other MLVs, too. Indeed, the "VRA" and "VRB" regions were previously recognized by the art, see e.g. Tailor (2000); infra.

Exhibit 2 is a multiple sequence alignment, made using the standard software package vector NTI with its default settings, of the sequences of all of the envelope proteins listed in Figure 1. It is quite evident how strongly the various residue positions are conserved.

Tailor, "A Comprehensive Approach to Mapping the Interacting Surfaces of Murine Amphotrophic and Feline Subgroup B Leukemia Viruses with Their Cell Surface Receptors", J. Virol., 74(1):237-244 (2000) (Exhibit 3) note that (1) receptor recognition by MLVs is determined by the amino terminal domain of the envelope protein, (2) the domain consists of several conserved regions interrupted by variable regions VRA and VRB, (3) VRA and VRB have

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[6] Revised WDTM Ex. 11A concedes that the concept of conservative substitutions, i.e., replacement within sets of similar amino acids known as exchange groups, was well known in the art.

been implicated in receptor specificity, and (4) the 3D structure of at least one MLV envelope protein was then known. Tailor explored the effects of substitution mutations in the VRA and VRB regions.

Sliva and Schnierle, "Targeting retroviral vector entry by host range extension" Gene Ther Mol Biol. 8:335-42 (2004) (Exhibit 4) provide a schematic structure of the Moloney-MLV envelope glycoprotein. (Fig. 1), including identification of the receptor binding domain. They state

> The receptor-binding domain (RBD) is located in the SU subunit of Env (Figure 1A, B). Two hypervarible regions (VRA and VRB) are believed to be the main determinants of the receptor-binding specificity. The structure of the receptor-binding region has been determined and the VRA and VRB regions form parallel a -helices that shape the receptor-binding site. The receptor-binding site is followed by the proline-rich region (PRR), which is thought to have a hinge function. The PRR has a role in stabilizing the overall structure of the protein, affects the SU-TM interactions and functions as a signal which induces the envelope conformational changes leading to fusion . The PRR contains a highly conserved N-terminal sequence and a hypervariable C-terminal sequence. The hypervariable region of the PRR has been described to be not absolutely required for envelope protein function . The C-terminal domain of SU is believed to mediate the SU-TM interaction (Figure 1B).
>
> A conserved motif (SPHQV) at the N-terminus of SU containing the histidine residue H8, has also been shown to be required for membrane fusion. Deletion or mutation of this histidine residue abrogates Env's fusion activity, but not receptor binding. Surprisingly, this fusion defect can be restored by adding soluble fragments of SU, containing the receptor-binding site, to viral particles carrying Envs with a mutated histidine (Zavorotinskaya and Albritton, 1999; Lavillette et al, 2000; Barnett and Cunningham, 2001).

> TM contains the hydrophobic fusion peptide (FP) at its N-terminus. It is crucial for membrane fusion and becomes exposed and inserted into the host cell membrane after receptor binding and the resulting conformational changes in Env. The fusion process also involves major changes in the membrane proximal region of TM. A six-helix bundle is formed, which pulls the cellular and viral membrane closer together, driving membrane fusion by permitting membrane merging and pore formation. This finally leads to fusion of the viral and cellular membranes, and eventual delivery of the viral core into the cell.
>
> The mammalian type C retroviruses, like MLV, can be divided into four different naturally occurring host-range subtypes according to the distinct cell-surface receptors they recognize among species as well as to the viral interference patterns. MLVs that recognize receptors found on both rodent cells and cells of other species are classified as amphotropic and dual- or polytropic viruses, while the receptor for viruses with xenotropic host range is present on cells of a variety of species but not on mouse cells. Receptors for ecotropic MLVs are restricted to cells of mouse or rat origin, which makes this envelope to a good candidate for targeting approaches. However, all receptors belong to the family of membrane transporter molecules . While this allows different host ranges for the various retrovirus family members, it also implies that the receptor's function might have an important task during viral entry.

Sliva then discusses extension of the ecotropic envelope host range by insertion (usually more disruptive than amino acid replacement) of amino acids defining a foreign receptor-binding ligand. The sites discussed are the N-terminus of SU, the proline-rich region, and the Cys73-Cys81 loop of the RBD.

While Sliva was published in 2004, we believe that the quoted excerpt reflects information known in the art as of our priority date (cp. Tailor, supra).

Applicants clearly contemplate and teach the value of

comparing the SL3-2 sequence to that of MCF-247 and other MLV.

Fig. 1 of course makes this comparison for the VR3 region for SL3-2 vs. 29 other MLV, and Fig. 2 for the entire sequence vs. MCF 247.

Mutations in VRA, VRB or VR3 are more likely to change tropism (e.g., by affecting attachment and fusion) than to be generally disruptive or neutral.

Applicants state on P33, L3-23:

> Alignment of MLV envelopes shows almost perfect homology in this region between polytropic, xenotropic and amphotropic sequences. It is possible that this segment plays an important role in mediating fusion by Env. Since the receptor for polytropic/xenotropic viruses differ from those for amphotropic viruses, the function of the VR3 segment might be independent of the receptor binding. This idea is confirmed by the fact that this region is outside the receptor binding domain of amphotropic and ecotropic envelopes (Battini *et al.*, 1992), (Heard *et al.*, 1991).
>
> In apparent disagreement, the entire N-terminal segment of polytrophic and xenotropic envelopes including the (polytropic or xenotropic but not amphotropic) proline rich region is necessary for envelope function (Battini *et al.*, 1992), (Battini *et al.*, 1995). Polytropic and xenotropic N-terminal fragments of SU cannot confer superinfection resistance unless they also include the proline rich region, but the proline rich region neither binds the receptor on it own

> nor changes the tropism of the amphotropic envelope if it replaces amphotropic PRR.
>
> These data suggest that the binding domain of polytropic and xenotropic envelopes are longer than that of ecotropic or amphotropic envelopes and also include the proline rich region. It is also possible that VR3 and proline rich region of polytropic and xenotropic envelopes are important in correct folding of the receptor binding domain and are not directly involved in binding the receptor.

Nor did applicants merely compare SL3-2 with MCF-247 and its relatives. They made some specific mutations within VR-3.

First, as shown in Table 4, they make a series of chimeras in which a particular region of the SL3-2 envelope was replaced by the corresponding (see Fig. 2) MCF-247 sequence. The affected regions were the Leader, VRA, VRB and VR3 regions. Three of the chimeras (S/M Leader, S/M VRA, S/M VRB) satisfied claim 4, activity (a), i.e., they were capable of mediating infection in NIH 313 and Psi2 cells, hence presumably using the receptor recited in 1(a), but not in human TE671 cells.

These three chimera differed at, respectively, 2, 3, and 6 amino acids from SL3-2 (Fig. 2).

The fourth chimera (S/M VR3) was additionally able to mediate infection of humans TE671 cells and thus satisfied 4(b). It can be seen from inspection of Figs. 1 and 2 that this S/M VR3 differs at <u>five</u> positions (199, 200, 202, 212 and 213) from the native VR3 of SL3-2.

In view of the inability of the leader, VRA and VRB chimera to mediate infection of human cells, it could be assumed that tropism toward human cells was <u>not</u> mediated by any of the VRA or VRB amino acids at which SL3-2 and MCF247 differed. That left

VR3. As stated at P30, L4-6:

> Among the amino acids in the VR3 region, there are five that are different between SL3-2 and MCF 247. Any combination of these can be responsible for the different tropisms of these viruses.

Applicants then prepared a combinatorial library allowing 32 possible sequences; in essence, at each of the five VR3 variable positions, the polypeptide could randomly exhibit either the SL3-2 choice or the MCF247 choice. Thus we had 199A/G, 200S/P, 201A/V, 212R/G, and 213T/I.

34 colonies producing envelope proteins putatively capable of infecting TE671 cells were sequenced, with the results shown in table 5. There were 14 unique sequences, and it is interesting to note that these didn't include the S/M VR3 chimera sequence, with the five variable AAs being Gly199/Pro200/Val302/Gly212/Ile213). (Note that a few colonies were outside the planned range of sequence variation[7], attributed to inaccurate primer synthesis; P32, L6-10).

Table 5 does include the wild-type SL3-2 sequence (last row of table). The wild type sequences in table 5 (and in table 7) are "background" that can result from:

(i) the very low infectivity of the wild type on human cells (the wild type has a titer of less than 1 cfu/mL, but it is not zero);

(ii) different sources of contamination in cell culture or PCR products;

(iii) "hitchhikers" from producer cells that are infected by a multiplicity of infection (moi) of more than one. If one producer cell in the library is infected by, for example,

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[7] Ser or Thr at 199, and Ser at 212.

both the wild type and a mutant then the mutant virions can package the wild type genome and carry it over.

Therefore the library results are more interesting from a statistical point of view. However, to address this issue, we tested several individual clones with different VR3 loops to establish whether the isolated clones from the libraries were indeed infective on human cells.

The applicants examined the positions to see which were biased toward MCF247, and thus were likely to be "the determinants for the different tropisms of SL3-2 and MCF247 viruses". (P32, L2-5). We rearrange the table at the top of P32 to make this clearer:

Position	SL3-2 choice	MCF247 choice	Other
199	55% (Ala)	33% (Gly)	T,S
200	60% (Ser)	40% (Pro)	-
202	51% (Ala)	49% (Val)	-
212	6% (Arg)	94% (Gly)	-
213	15% (Thr)	85% (Ile)	-

Several differed at three positions from SL3-2, e.g., TSAGI (199, 200, 202, 212, 213), GSVGI, GPAGI.

Applicants concluded that "the first three amino acids showed a more or less random choice of amino acids". While that meant that it was positions 212 and 213 that were responsible for the human cell tropism (or lack thereof). It does not diminish the importance of the mutation of positions 199, 200 and 202 vis-a-vis the issue of whether there is written description for the claimed genus.

The unexpected appearance of serine and threonine at position 199 is commented on at P42, L21-P43, L12. In Table 6, the human and mouse tropism of wild type (RT) and mutated (TT, GT, GI) positions 212-213 was quantified. This led to the conclusion that the major determinant of the limited tropism of SL3-2 having only a secondary effect (P32, L28-29).

In Table 7, applicants prepared a combinatorial library with a sequence space of 400, i.e., positions 212 and 213 could each be any of the 20 genetically encoded amino acids.

28 colonies that putatively expressed mutant envelopes mediating infection of human cells were selected (see table). At position 212, 48% had Met, 14% Gly, and 16% Leu. Cys, Gln, Arg, and Ser were also represented. At position 213, 48% had Val, 12% Ala, 8% Leu, but His, Phe, Lys, Trp, Thr, Arg, and Gly were also represented.

There are 17 different unique single or double substitution mutants identified as functional by table 7. Only the Arg-Thr (wild type SL3-2) had previously appeared in table 5, so 16 of these are new.

The tropisms of 14 of these mutants, together with SL3-2 and MCF247, were quantified in Table 8. It can be seen that the MV mutant was superior even to the GI mutant inspired by MCF247, as commented upon at P38, L4-7.

Table 8 quantifies the effect of the SL3-2 (GI), (LI) and (MV) mutants on two other human lines, He La and 293.

Table 9 shows that the three SL3-2 mutants of Table 8 use the same receptor (Rmc1) as the MCF virus.

The showing made in this application plainly exceeds what is required by revised WDTM Example 11B. Example 11B postulated that a specification disclosed data from deletion studies that identify two domains as critical to activity Y, i.e., a binding domain and a catalytic domain. The specification proposed that conservative mutations in these domains (e.g. one basic amino acid substituted for another basic amino acid) will still result in a protein having activity Y, while most non-conservative mutations in these domains will not result in a protein having the recited activity. The specification also proposed that most mutations, conservative or non-conservative, outside the two domains will not affect activity Y to any great extent.

The PTO also assumed that only a single species within the claim had been reduced to practice.

The PTO acknowledged that the specification failed to teach exactly which of the polypeptides with at least 85% identity to the reference sequence would have the required activity.

However, it was willing to accept that the identification of domains responsible for activity Y established a structure-function correlation that showed where non-conservative substitutions would be tolerated, i.e., outside these domains. It also accepted that many of the possible conservative substitutions would be tolerated.

It is clear that the present applicant explicitly taught which residues were conserved as between SL3-2 and MCF-247 and hence more likely to be necessary for "basic" envelope function (Fig. 2). Applicant's also identified 28 additional functional envelope polypeptides of known sequence (Fig. 1) and these sequences could readily have been compared by the sequence alignment methods disclosed on pp. 8-9.

While there is no explicit formal definition of conservative substitutions in the specification, there is implicit recognition of the concept (which is in any event well known to molecular biologists, as the Revised WDTM admits). Thus at P6, L17-21, applicants allude to the difference between percentage identity and percentage similarity[8]; a conservative substitution is of course the replacement of an amino acid with a similar one. Such sequence similarity is effectively quantified by the scoring matrix used by sequence alignment software, such as the default scoring matrix used by blastp (P6, L29) at the file of filing. Similar amino acid pairs are those with positive scores in this scoring matrix.

Applicants of course were concerned less with "basic" envelope protein activity and more with control of its tropism, i.e., in particular its ability to mediate infection of human cells.

They identified the VR3 region as critical to the difference

[8] New claim 54 is based on P7, L18 as modified by P6, L17-21.

in tropism between SL3-2 and MCF247, and by mutational studies determined that positions 212-213 were the most significant.

Unlike the model specification of revised WDTM Ex. 11B, in which only one active sequence was reduced to practice, applicants have reduced to practice many different polypeptides

(a) capable of mediating infection vs. mouse but not human cells	(b) capable of mediating infection of human cell
SL3-2 WT (Sid 2) S/M Leader chimera S/M VRA chimera S/M VRB chimera RI mutant from Table 6 RA and CR mutants from Table 8	S/M VR3 chimera GT and GI mutants from Table 6 remaining 10 mutants from table 8[9]

We further wish to point out that even though in WDTM Example 11B the model specification made various comments as to how to mutate the protein inside and outside the identified domains, the PTO did not require that the claim explicitly allow only conservative substitutions within the domains. Likewise, it is inappropriate for the examiner to require applicants to limit non-conservative mutations, let alone all mutations, to VRA, VRB and VR3, let alone to VR3 or in particular amino acids 212-213. That said, please note new claims 51-53 and 55. (Re claim 55, note P4, L17-20).

Applicants are in "possession" of SL3-2 mutations, both mutations that are reasonably expect to alter tropism (i.e., those featuring mutation at 212-213), and those that are of what might be termed a "gratuitous" nature; i.e., mutations not expected to abolish activity, which applicants must cover by

[9] Mutants of Table 8 assigned to (a) or (b) depending on whether activity vs. human Te671 exceeded 10^2.

their claims lest competitors enjoy the benefit of applicant's discovery of SL3-2 without any obligation to take a license from applicants. The 95% (and higher) identity limitations act as a constraint that ensures that the claims remain commensurate with applicants' contribution to the art.

That said, we note that besides the claims with higher percentage identity limitations (43-45 and new claim 50), several other claims require particular sequence structures and hence require separate consideration by the examiner. These include

9 (Ind): requires at least that AA 212 is Met

47 (Ind): requires WGLRY and DP, separated by 5 amino acids

48 (4): requires the VR3 region of SID2

49 (4): requires that AA 212 is Met.

Respectfully submitted,

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Enclosure
-Exhibit 1: Brochieri, et al. 2005
-Exhibit 2: multiple sequence alignment
-Exhibit 3: Tailor (2000)
-Exhibit 4: Sliva (2004)

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